Author's Response

Epidemiology between astronomy and astrology

From WASIM MAZIAK

I thank Vandenbroucke, Pearce and Douwes for their enriching commentaries on my article.\(^1\)\(^-\)\(^3\) I feel the need though to respond to Pearce and Douwes because they made me say what I did not, and because of what appears to me their state of denial regarding asthma research. Dunn’s letter, however, merits response only to highlight the confusion resulting from mixing dogma with science. Foremost, I wrote my article because I care about epidemiology, so I do not understand why Pearce and Douwes thought that I am condemning epidemiology, epidemiologists or asthma epidemiologists for that matter.\(^1\) I also advanced the evolutionary perspective in the context of providing guidance for complex disease/small risk epidemiology by highlighting specific areas where such perspective can be helpful.\(^1\) I certainly did not attempt to sell this perspective as providing a fundamental role for future epidemiological research, or as a magic wand that can create ready answers for major public health problems of the 21st century, as implied by Pearce and Douwes.\(^3\) In fact, I highlight in my article the complexities involved in aligning this perspective with the genetic epidemiology of chronic disease. This is because of the complex fitness landscape related to multiple gene–environment interactions involved in chronic diseases, as well as the tradeoff between numerous traits within phenotypes—the units of natural selection—with their greater underlying genetic diversity.\(^1\) In essence, considerable genetic diversity for complex traits can be maintained within the population even in the face of strong selection forces,\(^1\) which greatly complicates the translation of the evolutionary perspective into working hypotheses for the study of complex diseases.

The relevance of the evolutionary perspective for the study of chronic disease, however, stems from the understanding of the health price resulting from the spread of behaviours (e.g. food over-consumption, low physical activity) that are so different from the ones that shaped our natural selection.\(^1\) Historical and archeological evidence shows that hunters-gatherers were generally lean, fit and largely free from chronic diseases.\(^4\) Moreover, when traditionally living populations adopt western lifestyles, obesity, diabetes and cardiovascular disease become commonplace.\(^5\)\(^-\)\(^6\)

Generally, our craving for energy-dense foods and efficiency in conserving and storing excess energy intake worked well to our advantage when food was scarce and rigorous physical activity was mandatory for survival, but perhaps has turned deadly in an environment of food abundance and optional physical activity. This fundamental concept is often absent from studies trying to provide statistical justification for assumed ‘healthy’ prescriptions, or to manipulate behaviours that are inscribed in our survival code (e.g. intervention aiming at changing the eating habits of people rather than food/physical activity environment). So Pearce and Douwes’s\(^3\) assumption that forces of selection work primarily on factors that affect the reproductive life-span (i.e. will not affect susceptibility to chronic disease) can be incomplete. Our genome may not be optimally selected to prevent chronic disease under Paleolithic conditions, but it is fitted for behavioural adaptations that rendered us susceptible to chronic disease under current environments. In addition, for a social species like humans, one can argue that individual’s reproductive success can depend considerably on the resources of the community-clan-family such as reciprocity and altruism, including the contribution of the wisdom/experience of the elderly.\(^7\)

However, the main thrust of Pearce and Douwes’s article, and its main divergence from my view, lies in their appraisal of the value of asthma epidemiological research of the past two decades. Certainly, the descriptive part of asthma epidemiology and international comparisons have contributed to the worldwide surveillance of asthma.\(^8\)\(^-\)\(^9\) But unlike the original promise, such vast descriptive workload did not lead to hypothesis generation or credible etiological leads that could pass the test of analytical or experimental studies (case control, cohort, randomized clinical trials).\(^1\)\(^-\)\(^3\)\(^)\(^10\) Pearce and Douwes\(^3\) defend the validity of this approach by tracing it back to the epidemiological study of cardiovascular disease and cancer in the 1950s. One of the main points I try to make in my article, however, is that while this approach have contributed a lot to the uncovering major risk factors (e.g. smoking, hypertension), it is not expected to work with complex/small risk factor diseases such as asthma.\(^1\) In fact, Pearce and Douwes\(^3\) acknowledge the complexity of asthma at every level from clinical manifestations, to the underlying pathology and triggering factors, and finally to the different life-course phenotypes. Yet they insist that a one-page questionnaire can be a valuable tool for the epidemiological study of asthma etiology as exemplified by the ISAAC study.\(^3\) Methodologically speaking, noise in the assessment of outcome or exposure can be tolerated when the risk estimate is huge and its mechanism of action is fairly predictable, while such

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noise can throw the results of epidemiological investigation in any direction for small and complex risks that are poorly understood.  

As for the public health relevance of asthma research, I really do not believe that Pearce and Douwes seriously think that raising children on a farm or in low-prevalence country or with a cat in the house represent achievements of asthma research, especially when the mechanisms involved in such "protective" effect are not clear.  

The fact that we have not moved very far from Blackley’s original observations (1873) about the low prevalence of hay fever and allergy among farmers is very telling about the current status of asthma research. The same goes for the recognition of non-allergic part of asthma, highlighted by Pearce and Douwes as another achievement of asthma research of the past two decades. When I studied medicine in the early 1980s, we were introduced to two main types of asthma: extrinsic (allergic) and intrinsic (non-allergic), and while we have now more elaborate models of these types, I do not see us making major breakthroughs in this regard from a public health point of view. Actually, where applicable, the allergic paradigm of asthma has still more to offer in terms of public health intervention than the hygiene model in its various interpretations.

Finally, Pearce and Douwes’ recollection of that evening in the bar tells a lot about the story of asthma research, whereby contradiction prevails and inconvenient findings do not get published. And had the evening been longer, I am sure that more examples of incidental and interesting findings of asthma-related factors would have emerged. I had a related experience at the end of asthma session at the annual meeting of The International Society for Environmental Epidemiology in Garmisch-Partenkirchen (2001), where I asked a panel of leading asthma researchers, after listening to some good dose of conflicting evidence about potential protective/risk factors of childhood asthma, whether this situation takes us back to square one and invites us to re-examine our tools and guiding principles in asthma research. The answer was that my position reflects a skeptical way of summarizing asthma research, and that the way forward is to share any suspected factor/s between researchers who have large databases of childhood asthma, so others can run it through their databases until a universal culprit/s emerges. Well, two decades of extensive collection/exchange of leads and probing of databases have elapsed, but as Pearce and Douwes rightly acknowledge not a single target (yet) for intervention has resulted. It is an approach similar to continuing to draw lottery numbers until hitting the jack-pot, or in terms of other scientific fields an approach that is closer to astrology than astronomy. This is why I stress, and asthma here is just an example, that wading into the era of complex disease/small risks with the tools and mentality of major risk factors epidemiology has lead us nowhere.

As I clearly indicated in my article, I see an increasing and more important role for epidemiology in making sense of the risks associated with the drastic changes in our lifestyles and environments. Recognizing the great contributions of Pearce and Douwes to epidemiology, an essential step to fulfill this promise lies in our ability to retain self-criticism and to continuously revise our tools and concepts. Dunn’s letter, on the other hand, demonstrates how a biased reading can result from mixing one’s own beliefs and emotions with scientific concepts and arguments. I was clear in my article how an evolutionary perspective can guide our study and interpretation of small risks of complex diseases, and certainly did not call for an evolutionary genomic research agenda as Dunn misinterprets me. On the contrary, I make it clear in my article and response above, that due to evolutionary considerations, the study of gene-environment interactions may not easily deliver on the promise of advancing our understanding of complex diseases. And I am certainly not crazy to suggest an evolutionary epidemiological study with a time span adequate to elicit the influence of natural selection on our genome. But the ideological stance underlying Dunn’s response becomes apparent when he declares that ‘evolutionary theory is trans-science because even the strongest advocates of evolution admit it cannot be studied’, which is a common jargon among anti-evolution creationists. I believe it is not the place here to debate the unequivocal scientific evidence in support of the evolutionary theory, its central role in all biological sciences, or the variety of approaches applied to support such a historical theory other than Dunn’s naïve requirement of a trans-generational study. Also, the meaning of ‘theory’ in the scientific context does not imply a hierarchy in confidence compared with facts as Dunn’s camp tirelessly try to portray. There are numerous hypotheses with the same type of substantiating evidence as evolution (e.g. continental drift and plate tectonics), yet they are widely accepted and do not attract much scrutiny from conservative positions for reasons that have nothing to do with the strength of their supporting evidence, but because they are not perceived to represent a threat to religious doctrines. Disguising a religious stand in a ‘scientific opinion’ does not advance the arguments about the future of epidemiology.

References
We do not consider that we have misrepresented Dr Maziak’s views as expressed in his original paper, but we nevertheless thank him for this further clarification of them. Most of the issues raised by Dr Maziak in this further correspondence were addressed in our previous paper, but we would like to take this opportunity to expand on ‘our state of denial regarding asthma research’ and whether an evolutionary perspective will provide the missing link to move epidemiology ‘from astrology to astronomy’.

As noted previously, we agree with many of Dr Maziak’s criticisms of the current state of asthma epidemiology. However, we do not agree that initiatives such as the ISAAC study are examples of ‘worst practice’; rather we see them as examples of ‘best practice’ that are playing a key role in the development of the field. In fact, it has been repeatedly demonstrated that symptom questionnaires, such as those used in the ISAAC and ECRHS studies, validate well against clinical asthma, and have superior validity to that of supposedly more ‘objective’ measures such as bronchial hyperresponsiveness (BHR) testing. A major strength of such questionnaires is that they can provide valid prevalence estimates, and thus promote further research and debate, even while the complex underlying aetiology of asthma is poorly understood. In particular, they allow for comparisons of populations with clear contrasts in the prevalence of asthma and protective exposures, e.g. comparisons between high- and low-income countries or between farming families and the general population. In contrast, more ‘objective’ measures such as BHR testing are less feasible for international comparisons, and require (probably invalid) assumptions about the underlying aetiology of asthma, which may be why they validate less well than symptom questionnaires in general population samples.

This does not mean that symptom questionnaires are infallible instruments, but rather that they have reasonable validity, and are the best available for their intended purpose. In this context, we can only re-emphasize the major role that the ISAAC and ECRHS studies are playing in questioning established dogmas, and re-orienting our thinking as regards to asthma aetiology, by showing that the established theories may work well in the laboratory, but do not work so well in, for example, Latin America.